Heterozygote advantage for the phenylketonuria allele

SIR,

We wish to comment on Dr Saugstad's paper (Saugstad, 1977) in which she reports that the birthweights of Norwegian children with phenylketonuria are lower than the birthweights of their unaffected sibs, and that the latter have higher birthweights than the general population. Dr Saugstad suggests that this birthweight pattern confers on the heterozygote carrier of the phenylketonuria gene a selective advantage over individuals with normal genes (Saugstad, 1972, 1975, 1977).

We have been unable to confirm Dr Saugstad's findings in a study of 56 families containing at least one child with and one without phenylketonuria. The cases of phenylketonuria, all of whom attend The Hospital for Sick Children, London, were of classical biochemical type; in 33 of the families the index case presented with mental retardation. The results of this study are presented in the Table. There is no significant difference between the mean birthweights of the children with phenylketonuria and their normal sibs, and the male sibs are on average smaller than the males with phenylketonuria. Both resemble the mean of the general population of 40 weeks' gestation (British Perinatal Mortality Survey, 1969). The obstetric notes were not readily accessible to us, so no adjustments could be made for gestational age. The clinical histories did not, however, suggest a high incidence of prematurity or obstetric abnormality and only 3 phenylketonuric and 1 sib were known to have been born before 38 weeks.

Sib size varied from 2 (1 child with phenylketonuria and 1 unaffected) to 11. In the general population

there is a significant family (Tanner *et al.*, 1972) and birth order (Tanner and Thompson, 1970) trend in birthweight. To avoid any bias from this cause the birthweights were first adjusted (assuming that all infants were of 40 weeks' gestation) for male sex and second or later birth (Tanner and Thompson, 1970), and mean figures for the birthweights of the phenylketonuric and for the normal children were calculated for each family. The means of these adjusted figures (Table) are similar for the phenylketonuric and normal children, though they fall below the expected general population mean (3.56 kg) for male infants of second or later birth at 40 weeks' gestation. This can be explained by the failure to make allowance for gestational age in the sample.

We are, therefore, unable to confirm Dr Saugstad's observation of an increased birthweight in the unaffected sibs of patients with phenylketonuria. Another recent study has also failed to confirm this finding (Rothman and Pueschel, 1976). It would be of interest to know whether the high mean birthweight of the sibs in Dr Saugstad's sample persists if adjustments are made for family influences and birth order.

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Table Mean birthweight in children with phenylketonuria and in their unaffected sibs

	Actual				Adjusted (for sex, birth order, and family)			General population* (40 weeks' gestation)	
	No. cases	PKU	No. cases	Sibs	No. families	PKU	Sib	All births	Males, second or later birth
Girls	28	3.34 (0.61)	48	3.37 (0.61)	56	3.43 (0.57)	3.47 (0.48)	3.34 (0.45)	3.56 (0.44)
Boys	48	3.44 (0.61)	58	3.33 (0.57)				3.50 (0.47)	

*British Perinatal Mortality Survey (1969).

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This letter was shown to Dr Saugstad, who replies as follows.

SIR,

The increase in mean birthweight with parity has usually been taken to indicate an increase in birthweight in individual families from the first- to the second- and later-born children. However, increasing birthweight with increasing birth order may not be the rule in individual families in Britain today.

Between 1958 and 1970 mean birthweight in England and Wales declined from 3400 g to 3367 g for male and from 3260 g to 3249 g for female neonates (Chamberlain *et al.*, 1975). The proportion of heavy neonates (>4000 g) declined from 9.3% in 1958 to 8.2% in 1970, simultaneously with an increase in the proportion of neonates weighing between 3001 and 3500 g from 35.9% to 39.0%. This decline in mean birthweight and proportion of heavy newborns is most probably the result of several factors. Primarily we may focus attention on the significant rise in induction of labour in the same years. From an initial level around 13% in the early 1960's (Richards, 1975, 1977) when there were clear medical indications for inducing labour: to allow a pregnancy to proceed naturally would carry risks to either the mother or fetus or both (postmaturity, fetal distress, toxæmia, etc.), the proportion of induced labour now (1974 to 1977) amounts to 40% or more. The present induction policies obviously differ from the previous ones and an unknown proportion of deliveries are probably induced preterm as well as with no medical indication. Among other important factors are the increased use of dietary restrictions in pregnancy and in the use of diuretics during the past 10 years or so (Blumenthal, 1976; Campbell and MacGillivray, 1975, among others). Both these factors affect fetal growth rate. With free abortion in Britain, we have also to consider the possible growth-retarding effect of a previous pregnancy terminating with an abortion.

In Britain today several second- and later-born children may, therefore, not show the previous characteristic heavier birthweight in comparison with

their firstborn sib. Birthrank is thus only slightly associated with birthweight. This observation has already been confirmed from the USA (Rothman and Pueschel, 1976, $r = 0.10$). In the present situation in Britain, when only about 50% of the deliveries are allowed to proceed naturally and with a constant increase in the various iatrogenic factors affecting fetal growth rate, an observation of a slight or lack of correlation between birth order and birthweight in individual families tells little about the true intra-uterine rate of growth in the mothers involved. This applies equally to families with affected offspring as well as to a control series. In investigating intrafamily variation in birthweight in Britain today accurate observation from the maternity hospitals including birthweight, length of gestation, and detailed information on pregnancy and delivery is a prerequisite. In addition, if there is at present in Britain no significant association between birth order and weight at birth such as was the case previously, application of a sophisticated technique of adjusting all birthweights to second-born and male, etc., as suggested by Smith *et al.*, is not only unnecessary, it is incorrect.

In Norway, in contrast to the case in Britain, there is a continuous upward trend in birthweight and a particular increase in the proportion of heavy newborns (Saugstad, 1977b). For instance, the proportion of neonates with a weight at birth of 4000 g or more increased from 16.4% between 1967 and 1971, to 16.7% of all births 1972 and 1974, concomitantly with a reduction in the proportion of neonates weighing 3000 g or less from 16.5% to 16.1%. Now more than half the neonates have a weight at birth of 3500 g or more (51%) as compared with only 35% of British neonates in 1970. With a proportion of induced labour of 11.8% for the years 1967 to 1971, the great majority of pregnancies are allowed to proceed naturally. In contrast to Britain, Norway has thus escaped the recent epidemic of induced labours. As evidenced from the rising proportion of heavy newborns it has also escaped the present widespread use of dietary restriction and of diuretics in pregnancy characteristic of the USA for several years and in recent years also of Britain.

In all births in Norway 1967 to 1968, mean birthweight increased from first- to second- and later-born (Fig. 1 (Saugstad, 1972)). A particular investigation of 47 well-to-do families with 4 or more children born in Oslo 1949 to 1970, described a standard deviation in birthweight of 7.9% of the sibship mean and confirmed an association between birth order and weight at birth with a mean difference in birthweight between the first two children of 9.1% (Saugstad, 1977a). There is also an association between birth rank and weight at birth as regards the PKUs born in Norway 1940 to 1973. This is, however, not the case with the

Fig. 1 Mean birthweight for first-, second-, and later-born PKUs, their non-PKU sibs, and controls (66 153 Norwegian babies). (Reproduced by kind permission of *The Lancet*, 1972.)

non-PKU sibs whose mean weight at birth increased only negligibly with parity, but was constantly well above the corresponding parity mean of the controls as well as of their PKU sibs. With a mean parity of 2.25 for the non-PKUs as compared with 2.24 in the control series (2.88 for the PKUs) and no particular deficit in firstborns among the non-PKUs (32.6% as compared with 36.9% of the controls and 26.5% of the PKUs) or any striking excess of higher parities (36.0% of non-PKU were later-born, as compared with 33.3% of the controls and 44.9% of the PKUs (Table 2, Saugstad, 1977a)), any adjustment for parity differences between the non-PKU sibs and the controls was not considered necessary.

In conclusion, the observed intrauterine growth potential of the Norwegian heterozygotes for PKU with affected offspring born in Norway between 1940 to 1973 is, therefore, considered to a large extent to reflect their true intrauterine growth potential. It ought to be mentioned, however, that in several families after the birth of an affected child abortions were induced before the birth of another child. This could have impaired fetal growth rate in later pregnancies. In contrast, taking into consideration the above-mentioned predominance of different iatrogenic interventions in pregnancy and delivery in Britain during the past 10 years or so, the intrauterine growth potential observed in the present series of PKU heterozygous mothers from London (year of birth of offspring not known) is not considered truly to reflect

their intrauterine growth rate. The two series are, therefore, not directly comparable.

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Sir,

In reply to the comments of Dr Saugstad on our letter of 26 May, subjects of our study were born between 1955 and 1973; 7 children with phenylketonuria and 6 sibs were born between 1970 and 1973. Tanner and Thompson's figures were collected before 1970. Data collected from British infants in 1970 (*British Births, 1970*) show that the difference of approximately 150 g between the birthweights of first and later born children was still present. Induction had a relatively small effect on birthweight in Britain in 1970 and cannot explain the difference between our results and those of Dr Saugstad.

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